## REMARKS

Reconsideration of this application is requested. Claims 1-15 are active in the application subsequent to entry of this amendment.

Minor changes have been made to claim 7 responsive to the examiner's comments in item 2 of the Official Action.

Missing from the Information Disclosure Statement submitted on June 30, 1999 are copies of three documents which were inadvertently misplaced. Copies of these documents are attached together with an additional listing of these documents (only) on a modified PTO-1449 form plus the relevant fee to assure consideration.

The balance of the Official Action deals with two prior art-based rejections directed towards 1-7 and 8-15, the composition and process of making claims, respectively. The examiner's comments have been carefully reviewed as has the prior art and based upon applicant's observations and comments that follow it will be apparent that these documents are not suggestive of the subject matter defined by applicant's claims.

The present invention is concerned with compositions and procedures that yield sub-micron and micron stable particles of fenofibrate. The **compositions of this invention include combinations of natural or synthetic phospholipids, and one or more nonionic, anionic or cationic surfactants coated or adhered onto the surfaces of the fenofibrate particles**. The combination of phospholipids and surfactants allows the formation and stabilization of the sub-micron and micron size compound particles by modification of the surface and changes in hydrophilic, lipophilic and electrostatic interactions between particles.

Claims 1-7 are directed to pharmaceutical compositions composed of fenofibrate microparticles produced by applying energy to fenofibrate in the presence of phospholipid and surface modifier(s). These microparticles *consist essentially of* fenofibrate, a phospholipid and at least one surface modifier. The surface modifier or surface modifiers provide volume-weighted mean particle size values of the water-insoluble compound about 50% smaller than particles produced in the presence of a

phospholipid and without the presence of the surface modifier using the same energy input. Procedures for preparing these compositions are the subject of claims 8-15.

The Examiner states: "Duclos (Duclos '495) teaches a composition comprising water-insoluble active ingredient, such as fenofibrate, surface active agents, organic solvents, and phospholipids."

More specifically Duclos '495 teaches the following (note bold emphasis added to quoted text):

- Column 2, lines 17 – 24: "the production of a **solid dispersion of at least one therapeutic agent in a hydrophilic carrier** having enhanced solubility in an aqueous media **comprises dissolving at least one therapeutic agent in a volatile organic solvent containing a very hydrophilic polymer and evaporating the solvent to dryness to form a co-precipitate of therapeutic agent and hydrophilic polymer**."

- Column 2, lines 55-67, Column 3, lines 1-2: Duclos '495 defines solid dispersions as **"The solid dispersions are systems in which one or several active ingredients are dispersed in the solid state** (microparticular, even molecular) in an inert solid vehicle (Chiou et al). These solid dispersions have to be made distinct from mere mixture of powders designated under the name of physical mixture. Two methods are currently used for the preparation of solid dispersions: the method of melting/solidification which leads to the formation of co-melted—and **the method of dissolution/ evaporation which leads to the formation of co-precipitates**. A mixed method resulting from the combination of both preceding methods, is sometimes cited but appears to be seldom utilized. **The process of the invention utilizes the formation of co-precipitates by means of dissolution—evaporation."**

The components of the composition are defined in Duclos '495 as follows:

- Column 3, lines 2 – 3, & Column 6, lines 41-46: "The very **hydrophilic polymer** dissolved in the organic solvent preferably is a polyvinylpyrrolidone" …."a number of solid dispersions have been prepared by the method of melting/solidification and or by the method of dissolution/evaporation using five **hydrophilic excipients: saccharose distearate, polyoxyethyleneglycol 4000, polyvinyl pyrrolidone, citric acid, and phospholipids."**

- Column 10 – 19: "The **organic solvent** usually is a solvent which both **dissolves the very hydrophilic polymer and the active ingredient** while having a sufficiently high degree of volatility to be in a position to be after dissolution of the mixture, evaporated off without having recourse to--very strong, physical means--such as heat or vacuum. Such solvents are for example oxygenated solvents such as ethanol,

isopropanol, tetrahydrofuran, isopropyl ether, acetone, methy ethyl ketone, tetrahydropyran, or chlorinated solvents such as methylene chloride."

- Column 3, lines 21-26: "The **optionally added surface-active agent preferably is a non-ionic surface active agent** selected from the polyoxyethylenic esters of sorbitan and saturated or unsaturated fatty acids having at least 8 carbon atoms; polyoxyethylenic ethers of fatty alcohols of at least 8 carbon atoms and the polyoxyethylenic esters of stearic acid."

The Examiner states that Duclos '495: "... fails to specifically teach the claimed method to prepare said composition" presumably fenofibrate, surface active agents, organic solvents, and phospholipids. Applicant agrees with this statement, although in the examples in Duclos '495, Column 16, lines 49-59 and column 17, lines 13-25 is taught:

"IV-SOLID DISPERSIONS WITH FENOFIBRATE
1-Production of the solid dispersions of the invention
A-Raw materials
**Fenofibrate** (batch F 0092.times.100) from Schweizerhalt France-Deshors 17 Bd de Montmorency 75016 Paris, **polyvinylpyrrolidone** (Kollidon 30 - Nr 56 - 0902) from BASF AG 67056 Ludwigshafen Germany, **Tween 80 (polyoxyethylene sorbitan monooleate)** batch AB 397 (ICI Chemicals, Niederlassung der deutsche ICI GMBH, Goldschmidstr 100 D-4300 Essen 1) and absolute **ethanol**. ... **The solid dispersions were produced by evaporating under vacuum (P=205 millibars) for 25 minutes and then the pressure was decreased to its minimum (40 millibars) for 25 minutes. ... The samples with 2.5 g of fenofibrate had a yellowish appearance and formed a pellet more or less viscous after one hour of evaporation at the minimal pressure."**

The compositions described in 09/282,471; Parikh '471 (see above)

**"include combinations of natural or synthetic phospholipids, and one or more nonionic, anionic or cationic surfactants coated or adhered onto the surfaces of the fenofibrate particles".**

Several points distinguish applicant's claimed compositions and processes from that of Duclos '495. First, the present application (herein noted as Parikh '471) composition consists of "**sub-micron and micron size compound particles**" of fenofibrate (a poorly water-soluble compound) coated with phospholipids and selected

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surfactants. The Duclos '495 composition consists of a solid dispersion in the form of a co-precipitate containing the drug and a "**very hydrophilic polymer**". Although Duclos '495 claims phospholipid is a hydrophilic polymer, it is clear from many authoritative sources (See Attachment 1) that this is not the case, and that phospholipids are amphipathic, containing both a hydrophilic part and a lipophilic/hydrophobic part. The name "phospho**lipid**" reflects this lipid-like characteristic property. Also, the examples provided in Duclos '495 use undisputedly very hydrophilic polymers, such as polyvinylpyrrolidone. Duclos '495 does not provide an example using phospholipid, which applicant submits is not a "hydrophilic polymer". On the other hand, applicant provides several examples using fenofibrate and phospholipids in which the phospholipid adheres onto the surface of the water-insoluble or hydrophobic surface of fenofibrate.

The ability of phospholipid to adhere to the hydrophobic surface is a direct result of it being amphipathic. The hydrophobic/lipophilic part of the amphiphatic molecule is postulated to bind to the hydrophobic surface of fenofibrate crystals. Parikh '471 makes no use of very hydrophilic components. In fact the surfactants used are selected such that they contain a lipophilic portion and can absorb onto the surface of the hydrophobic fenofibrate. Because of fenofibrate's water-insoluble nature, these surfactants cannot be by nature "very hydrophilic polymers".

Thus applicant's compositions employ phospholipids and surfactants adhered to or coated onto the surfaces of the fenofibrate particles and not the "very hydrophilic polymers required by Duclos '495. The examiner will note applicants' claims specify compositions "consisting essentially of" the stated components thus exclude the "very hydrophilic polymers" of Duclos.

The physical nature of the composition described in Duclos '495 is fundamentally different from that in Parikh '471. Duclos '495 describes solid dispersions, also termed co-precipitates, of the active ingredient dispersed in an inert solid. Duclos '495 states that the precipitate can exist in a "microparticlular" form, but this is not defined. In Duclos '495 the inert solid is a very hydrophilic polymer. However, this composition could not exist in an aqueous environment because the very hydrophilic polymer would dissolve.

On the other hand, Parikh '471 teaches "microparticles" or submicron to micron sized particles consisting essentially of the water-insoluble drug fenofibrate coated with phospholipids and a selected surfactant, and that these particles exist in a stable form in an aqueous environment (see Examples in Parikh '471). A very hydrophilic polymer is not a component of the compositions claimed in Parikh '471 as applicant's claims clearly indicate. Thus applicant's claimed invention and Duclos '495 are two distinct inventions describing compositionally and structurally and functionally different products.

Ecanow (US Patent 4,963,367; Ecanow '367) in column 2, lines 14-24 states:

"While there are apparent similarities to the inventor's prior art, this application differs significantly in several important aspects. Thus, encapsulation is a fundamental aspect of the inventor's prior art and the present invention. However, **by polymerizing one or more of the surfactants used in the present invention**, and/or by modifying the previously disclosed processes, the proportion of the pharmaceutical component incorporated in the present formulation is approximately two to six times greater than that of formulations disclosed earlier."

Ecanow '367 claims in claim 1, column 41:

"A method of preparing a composition useful as a system to introduce and transport medically useful compositions in the body of mammals; said composition comprising particles of a coacervate-based matrix having one or more physiologically-active compound incorporated therein and a coacervative-based encapsulating film surrounding each particle; said method comprising forming a mixture of one or more surface active agents, water and one or more physiologically-active compounds to produce a two phase aqueous coacervate composition containing said compound, and emulsifying the composition to produce an aqueous emulsion of coacervate-based matrix particles containing the physiologically-active compound, said coacervate-based matrix comprising water selected from the group consisting of coacervate phase water, equilibrium phase water, and mixtures thereof, and said physiologically-active compound solubilized therein, said particles having an encapsulating coacervate-based film surrounding the particles."

Ecanow '367 further states in column 7, lines 31-57:

"... the compositions of the present invention are derived from a non-toxic two-phase aqueous coacervate system forming a matrix containing at least one polymerized surface active compound, one phase of which is colloid-rich, semipolar to nonpolar in character and capable of solubilizing (holding within the coacervate matrix) oil-soluble and water-insoluble components (coacervate phase); the second phase of the coacervate

composition is colloid-poor, semipolar to polar in character and capable of solubilizing (holding within the coacervate matrix) water-soluble and, to a lesser degree, water-insoluble compositions (equilibrium water phase). The polar phase of a coacervate composition is made of strong, dipolar molecules having hydrogen bonding, with dipole moments generally in the range from about 0.8D to about 1.85D. The semipolar phase is made up of strong, dipolar molecules that do not form hydrogen bonds, with dipole moments generally in the range from about 0.1D to about 0.8D. The nonpolar phase is made up of molecules have little or no dipole character, generally in the range of 0 to 0.1D. See Remington's Pharmaceutical Sciences, Mack Publishing Company, 1973, pp. 241-242. To a limited degree, however, the colloid-poor phase may be able to solubilize some apparently water-insoluble compounds, the colloid-rich phase being insoluble and in equilibrium with said colloid-poor phase."

Also, from column 13, lines 13-15, the coacervate phase is designed such that

"the drug ...(is)...solubilized in (held within the matrix of) the colloid-rich phase of the composition of the present invention."

Additionally, in Ecanow '367 in column 13, lines 27-30:

"In some instances ... the colloid-poor phase may be used to solubilize and prepare formulations of polar and semipolar drug compositions."

In column 1, lines 53-59, Ecanow '367 states:

"The method is based upon the use of a non-toxic aqueous coacervate; said method produces stable microemulsions comprised of particles in which one or more pharmaceutical components have been incorporated. Through the process of this invention particles are enveloped by a coacervate-based film."

In column 6, lines 15-19, Ecanow '367 states:

"...one or more physiologically-active compounds are encapsulated by an aqueous coacervate-based film **containing at least one polymerized surface active compound** to provide unexpected stability to the composition.."

In column 12, lines 45-48, Ecanow '367 states:

"**Drug compounds dissolved in any non-toxic, physiologically-acceptable solvent** such as a glycol, for example, propylene glycol, and/or alcohol also may be used in the practice of this invention."

In column 14, lines 49-51, Ecanow '367 states:

"Virtually **all surfactants useful to this invention can by polymerized** (e.g., modified fluid gelatin) and used in the method and compositions of the present invention."

In column 14, lines 55-58, Ecanow '367 states:

"To achieve the full advantage of the present invention, **the coacervate matrix includes at least one polymerized surfactant."**

In column 30, lines 3-5 (Example 7), Ecanow '367 states:

"The procedure of Example 1 is followed except that stroma-free hemoglobin **encapsulated in liposomes** comprises the hemoglobin component." Example 1 describes the use of monomeric lecithin, but the material produced **is encapsulated in liposomes**. Examples 14 to 21 also indicate the material is encapsulated in liposomes.

It is clear from the above quoted passages that the invention in Ecanow '367 relates to a solution of active (drug) ingredients in the colloid rich phase or coacervate phase. The coacervate phase is then emulsified in the colloid–poor aqueous phase to form "particles having an encapsulating coacervate-based film surrounding the particles" (Claim 1: column 41, lines 41-42) which contains "said physiologically-active compound **solubilized** therein". On the other hand Parikh '471 teaches "microparticles" or submicron to micron sized particles of the water-insoluble drug fenofibrate (i.e., the solid drug is **not** dissolved) coated with phospholipids and a selected surfactant. Parikh '471 teaches that these particles exist in a stable form in an aqueous environment (see Examples in Parikh '471). Also the process described in Parikh '471 does not use a coacervate-based process. Rather Parikh '471 describes a process involving the size reduction of the fenofibrate using prolonged exposure to significant forces (e.g. using high-pressure homogenization) in the presence of phospholipids and a second surfactant. Thus although both inventions teach methods and compositions for making submicron and micron sized particles, these particles are fundamentally different in their composition and physical structure.

Thus applicant submits that it is not obvious or indeed logically possible to prepare the composition and structure consisting essentially of fenofibrate, phospholipid and surfactant described in Parikh '471 in view of Duclos '495 and Ecanow '367. It should be noted that one skilled in the art, i.e., Duclos in '495, does not teach the current invention of Parikh '471 although Duclos had knowledge of Ecanow '367.

The examiner also states that "the cited references are silent as to the teaching of the claimed particle size values of the water-insoluble compound about 50% smaller than particles produced in the presence of phospholipid. It is the position of the examiner that no criticality is seen in the particular percentage since the prior arts obtain the same results desired by applicant, the microparticles of water-insoluble ingredient namely fenofibrate." The size of the microparticles of fenofibrate is critical in the present application, because an object of the invention is to overcome the fact that in its marketed form "it is poorly and variably absorbed and has to be taken with food" (Parikh first paragraph in "Background of the Invention"). By decreasing the size of the fenofibrate microparticles the surface area of the particles is increased. This in turn serves to increase the rate of absorption of fenofibrate and hence total amount of drug taken up.

Claims 8-15 are rejected under 35 U.S.C. 103(a) on the basis of the two references discussed above in combination with Haynes U.S. Patent 5,091,187 (Haynes '187) which in the abstract teaches:

"Water-insoluble drugs are rendered injectable by formulation as aqueous suspensions of phospholipid-coated microcrystals. The crystalline drug is reduced to 50 nm to 10 um dimensions by sonication or other processes inducing high shear in the presence of phospholipid or other membrane-forming amphipathic lipid. The membrane-forming lipid stabilizes the microcrystal by both hydrophobic and hydrophilic interactions, coating and enveloping it and thus protecting it from coalescence, and rendering the drug substance in solid form less irritating to tissue. Additional protection against coalescence is obtained by a secondary coating by additional membrane-forming lipid in vesicular form associated with and surrounding but not enveloping the lipid-encapsulated drug particles."

Further in Haynes '187 (Column 13, lines 45-60) it is stated that:

"**The primary requirement is that the coating lipid be membrane-forming**. This is satisfied by all lipids which, in the presence of excess water, make bilayer structures of the type which is well-documented for phospholipid vesicles or liposomes. **This requirement is not satisfied by fatty acids, detergents, non-ionic surfactants (e.g. polyethylene glycol) or triglycerides (vegetable oils, tristearin, "fats").** A secondary requirement is that the lipid not have a proclivity for converting into micellar structures. This excludes phospholipids of short chain length (6 or less) or lysolecithin (containing a single fatty acyl chain). High stability of the coating material in membrane form is necessary to keep the drug material from rearranging into macroscopic crystals. This is one reason why non-ionic surfactants do not work well for my intended purpose."

The Examiner states that "Haynes teaches a process to prepare water-insoluble microparticles comprising the step of size reduction by sonication, mixing drug with phospholipid and surface agent, and coating". However, on detailed examination of the patent it is apparent that integral to the invention in Haynes '187 is the primary requirement for the microcrystals "**that the coating lipid be membrane-forming**." Further Haynes '187 explicitly states "**This requirement is not satisfied by fatty acids, detergents, non-ionic surfactants (e.g. polyethylene glycol) or triglycerides (vegetable oils, tristearin, "fats").**" On the other hand Parikh '471 requires the presence of phospholipid "and at least one non-ionic, anionic or cationic surfactant". Thus the invention in Parikh '471 is surprising given the contraindicated use of surfactants in Haynes '187.

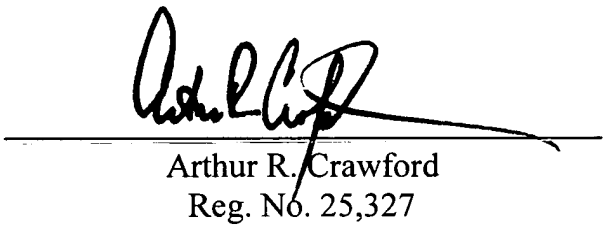
Given that Haynes '187 teaches that the non-ionic, anionic or cationic surfactant of Parikh '471 cannot be used in the method of Haynes '187, and given that the method of Ecanow teaches the active ingredient to be encapsulated in liposomes coated with one or more layers of a coacervate film comprising at least one polymerized surfactant and derived from a two phase aqueous coacervate system, and given that Duclos '495 requires use of phospholipids being considered as very hydrophilic components and that Duclos '495 being skilled in the art does not teach or anticipate the method of Parikh '471 in view of Ecanow '367, the method disclosed in Parikh '471 is therefore not obvious to those skilled in the art.

In summary, it is submitted that it is not obvious nor indeed logically possible to prepare the composition and structure consisting essentially of fenofibrate, phospholipid and surfactant as defined in applicant's claims in view of Duclos '495, Ecanow '367, and Haynes '187.

Reconsideration and favorable action are solicited.

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

By: 

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